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Machado, Flavia R.; Nsutebu, Emmanuel; AbDulaziz, Salman; Daniels, Ron; Finfer, Simon; Kisson, Niranjana; Lander, Harvey; Malik, Imrana; Papathanassoglou, Elizabeth; Reinhart, Konrad; Rooney, Kevin; Rüddel, Hendrik; Toccafondi, Giulio; Tulli, Giorgio; Hamilton, Vida

Published in:
Journal of Critical Care

DOI:
[10.1016/j.jcrc.2017.04.037](https://doi.org/10.1016/j.jcrc.2017.04.037)

Published: 01/08/2017

Document Version
Peer reviewed version

[Link to publication on the UWS Academic Portal](#)

Citation for published version (APA):
Machado, F. R., Nsutebu, E., AbDulaziz, S., Daniels, R., Finfer, S., Kisson, N., Lander, H., Malik, I., Papathanassoglou, E., Reinhart, K., Rooney, K., Rüddel, H., Toccafondi, G., Tulli, G., & Hamilton, V. (2017). Sepsis 3 from the perspective of clinicians and quality improvement initiatives. *Journal of Critical Care*, 40, 315-317. <https://doi.org/10.1016/j.jcrc.2017.04.037>

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SEPSIS 3 FROM THE PERSPECTIVE OF CLINICIANS AND QUALITY IMPROVEMENT INITIATIVES

Running title: Sepsis 3 and quality improvement

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Conflicts of interest: none

Funding sources: not applicable

INTRODUCTION

The Global Sepsis Alliance's Quality Improvement Committee (QIC) aims to collate sepsis quality improvement tools from different jurisdictions and resource settings onto the Global Sepsis Alliance (GSA) website for open access. The publication of the Sepsis-3 definitions resulted in a number of concerns related to its impact on the work of QI initiatives that focus on early identification and treatment of sepsis and prompted statements by the GSA, [HYPERLINK "http://www.global-sepsis-alliance.org" www.global-sepsis-alliance.org](http://www.global-sepsis-alliance.org) and the Surviving Sepsis campaign (SSC), www.survivingsepsis.org.

Thus, in this document we aim to assess the new sepsis definitions¹ in the context of quality improvement initiatives. We briefly describe the major changes and their potential advantages and disadvantages, in the context of the six domains of usefulness² used by the Consensus Definitions Task Force in creating the definitions, and from the point of view of two of the major stakeholder groups: those involved in clinical care and in QI programs.

WHAT ARE THE MAJOR CHANGES?

The 3rd International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) were published in February 2016.¹ The new definitions are intended to improve the clarity of definitions for clinical care, surveillance, quality improvement and audit, and research. The Task Force recognize that involved stakeholders might weigh differently relative importance of the six domains of usefulness of a definition (reliability, content validity, construct validity, criterion validity, measurement burden and timeliness).²

The new definitions were primarily based on clinical criteria (construct validity) and on their ability to predict outcome (criterion validity assessed by predictive validity) as assessed by a retrospective analysis of large databases from North America with a small contribution from one database in Germany.

Sepsis is now defined as “life threatening organ dysfunction caused by a dysregulated host response to infection”. The clinical diagnosis of organ dysfunction is made using the Sequential (Sepsis –related) Organ Failure Assessment Score (SOFA), with an increase in the score of ≥ 2 from baseline consequent to the infection being diagnostic. Where baseline is not known, it is assumed to be zero. The presence of systemic inflammatory response syndrome

(SIRS) criteria is no longer required for the diagnosis. Septic shock is defined as “a subset of sepsis with particularly profound circulatory, cellular and metabolic abnormalities associated with a greater risk of mortality than sepsis alone” The diagnostic criteria for septic shock are a “vasopressor requirement required to maintain a MAP of $> 65\text{mmHg}$ **and** a serum lactate level $> 2\text{mmol/L}$ in the absence of hypovolaemia”.

A new score was also described, the quick SOFA (qSOFA), developed as a bedside tool to rapidly identify adult patients with infection who are more likely to have poor outcomes. qSOFA is considered to be positive if the patient has at least 2 of the following clinical criteria: respiratory rate of 22/min or greater, altered mentation (Glasgow Coma Scale of <15), or systolic blood pressure of 100 mm Hg or less.

WHAT ARE THE POTENTIAL ADVANTAGES?

There are potential advantages in the new definitions:

- This was the first data-driven definitions set in which the domains of usefulness were used, helping to standardize concepts in the scenario of a heterogeneous syndrome such as sepsis.
- Consistency of language around definitions is likely to improve (severe sepsis and sepsis were commonly used interchangeably).
- The use of variation in SOFA score might help to identify worsening organ dysfunction in patients who already have documented dysfunction.
- SIRS criteria are no longer required for the diagnosis of sepsis. As approximately 10-12% of patients with sepsis do not have ≥ 2 SIRS criteria³ (at least in the intensive care unit (ICU)), the now historic use of SIRS criteria alone would have missed some patients with sepsis.
- The new qSOFA score uses signs such as high respiratory rate, low blood pressure and altered mental status that were found to be clinically relevant using a large database of patients with sepsis. Any one of these signs should be an alert to the bedside clinician to ‘think sepsis’, and as such qSOFA brings attention to the importance of any abnormal physiology in patients with infection. Altered mental status is increasingly recognized as a sensitive marker for severity of illness in sepsis.
- qSOFA and a change in SOFA score may be better predictors of poor outcome than offered by previous definitions

- The change may aid in the assessment of new therapies.

WHAT ARE THE POTENTIAL DISADVANTAGES?

There are also potential disadvantages in the new definitions:

- Using the new definitions in the clinical environment is likely to present difficulty, particularly as the SOFA score has not historically been used outside of the ICU (nor is it in routine and continuous use in all ICUs). This reduces the content validity of the new definition of organ dysfunction as most patients present to the Emergency Department or deteriorate on a ward. Those stakeholders will not recognize SOFA as a standard of assessment of organ dysfunction. As a result, non-ICU stakeholders might fail to engage fully with the largely ICU-driven new definitions.
- Complexity can lead to errors, which can lead to diagnosis and treatment variability. The current proposition adds burden to the data collection as well as for the bedside healthcare workers, since the complexity of calculating variations in six different organ dysfunction systems is high. Thus having SOFA variation as a definition also reduces its usefulness in the measurement burden, one of the relevant domains used to define usefulness of disease definitions.
- In terms of predictive validity, the variation in the SOFA score (which now defines sepsis) was validated comparing its ROC curve against the ROC curve of two or more SIRS criteria alone, rather than the previous definition of severe sepsis being SIRS criteria plus at least one organ dysfunction.
- There are major flaws in terms of construct validity. First, the current definition excludes patients with isolated hypotension or Glasgow 13-14 from the definition of sepsis as they will have a SOFA score of 1. Lactate is not part of the SOFA score, yet lactate is well documented as a sensitive marker of severity of illness in patients with infection, can identify 'cryptic shock' in patients who are normotensive, and the normalization of lactate levels with fluid resuscitation is a good prognostic indicator. As such lactate retains an important role in the risk stratification of patients with infection and in guiding initial fluid resuscitation as well as being a diagnostic criterion for septic shock.
- Health professionals on the front line in many countries now use track-and-trigger early warning score systems (e.g. NEWS, PARS) as a standard of care in identifying

potential deterioration or critical illness. Where used such scores, which are validated in their predictive values, have become the currency of communication around acuity of illness. To introduce a second aggregate score using similar variables with different thresholds (qSOFA) and which is specific to only one cause of deterioration not only adds complexity but also risks confusing organisational learning with potentially adverse consequence for patient safety in general.

- The weight given to predictive validity instead of to construct validity in the new qSOFA score is an issue. Using two of the three variables of this score as a prompt to act (e.g. refer to Intensive Care, transport to hospital) selects a population with a high risk of death and this risk of death is variable according to the different settings in which the score is applied. Additionally, the risk of death which is weighted acceptable, will vary according to their place of care, (out of hospital vs. in-hospital), the risk of not acting, and the ability to intervene effectively. Particularly in resource poor settings, but also in many high-income countries, the mortality rate associated with a qSOFA of 2 is unacceptably high to stand alone as a prompt to act. The requirement of two qSOFA criteria as a prompt to act might lead to the misunderstanding that patients with only one organ dysfunction or physiological derangement do not need timely appropriate escalation of care and treatment for their infection and organ dysfunction. This is not the intent of the new definition but it could be an unintended consequence. A single organ dysfunction or one qSOFA criterion attributable to sepsis warrants immediate diagnostic and therapeutic actions.
- The predictive validity used to generate qSOFA resulted in a severity assessment score, which is now being misused as a screening tool. Even its role as a severity score was not submitted to proper prospective validation in different settings. Recent studies indicate that qSOFA lacks sensitivity^{4,5,6}. Screening tools for sepsis require sensitivity to allow the capture of patients at risk of sepsis. Using qSOFA as a screening tool identifies patients with a high mortality and/or intensive care requirement- a qSOFA of 2 occurs at too high an acuity for many patients in hospital to first receive a higher level of care, and is of no value in determining whether a patient in the community requires hospital assessment. qSOFA is neither a diagnostic nor a screening tool for sepsis. At this moment, the qSOFA score cannot be recommended for wide scale use due to its lack of sensitivity. An unintended consequence of implementing this tool would be that those who do not fulfil its criteria might go without treatment. This is not its intended use. Patients with

infection or sepsis should have their infection treated as usual; the subgroup of patients who have two qSOFA criteria most likely require escalated treatment in an intensive care unit if available.

- Although we agree that the systemic inflammatory response syndrome criteria have a poor discriminant validity, SIRS still has an important role in identifying patients with infection who may benefit from antimicrobial therapy, fluids and additional screening for organ dysfunction. This approach has been used in many QI programmes with a positive impact on mortality reduction.
- The definition of septic shock requires a laboratory test, which is not available in many parts of the world mostly in low and middle-income countries (LMIC). This will preclude the diagnosis of septic shock in these settings and will generate a discrepancy in the criteria used around the world- this may compromise the epidemiological assessment of the sepsis burden. The Task Force, although acknowledging the issue, did not propose an alternative definition. The predictive validity of other signs of hypoperfusion was not assessed, thus they can not be used as substitutes for hyperlactatemia.
- The introduction of Sepsis 3 requires co-ordination with local and/or national coding practices.

THE IMPACT IN THE QUALITY IMPROVEMENT PROGRAMS

Operationalization of the new definitions

In terms of quality improvement initiatives, the major issue is the new definition of organ dysfunction. A variation in SOFA score is not a feasible tool to be used in the bedside identification of the potential septic patient. The broad definition of sepsis, the presence of a life threatening organ dysfunction, should remain the basis of all QI initiatives. Thus, screening for early identification and treatment of patients with sepsis (formerly called severe sepsis) should continue essentially as previously recommended by SSC and seek the presence of any organ dysfunction. We are fully supportive of the recent SSC statement recommending that patients with sepsis (formerly called severe sepsis) should still be identified by the same organ dysfunction criteria (including lactate level greater than 2 mmol/L). The new definitions should not change the primary focus- of early sepsis identification and initiation of timely treatment- in the management of this vulnerable patient population. qSOFA should

not be used as a screening tool for sepsis in wards or by emergency services before proper prospective validation.

National incentives to improve sepsis

Some countries have programmes and incentives to support improved sepsis management and enhance patient outcome. Achievement of agreed targets may have significant financial implications for hospitals under such programmes. Hospitals, other healthcare providers, commissioners and policy makers should ensure that any potential changes are co-ordinated with all the relevant stakeholders and that the targets and measurement processes are all aligned to ensure that the data is captured correctly and does not inappropriately affect the achievement of targets or the consequent resources.

Coding

The Task Force has made recommendations for coding based on the new definitions and ICD-10 codes. These need to be translated into practical instructions for clinical coders at a local or national level when sepsis-3 is being introduced to ensure data capture is optimised. Coders are not allowed to interpret laboratory data for organ dysfunction, or use SOFA scores to code for sepsis in patients with an infection diagnosis – coding for sepsis remains dependent on clinicians writing the diagnosis in the patient's clinical notes.

Change in sepsis population and impact on outcomes

Sepsis improvement projects should consider how implementation of the new sepsis definitions may affect their outcomes, as changes in outcomes may well be related to a change in sepsis population rather than true improvements in recognition and care. For instance, the Task Force did not clarify how the diagnosis of septic shock should be made in settings where lactate measurement is not available. In some areas, patients with hypoperfusion in the absence of vasopressors might be scored (in our view) erroneously under the 'sepsis' label; in other areas the same patients might be coded as having septic shock. If patients in areas without the ability to measure hyperlactatemia are considered as having septic shock, the mortality comparison between settings will be compromised as in

other settings vasopressors and hyperlactataemia will be required. If those patients are considered as having sepsis the incidence of septic shock in Low and Middle Income Countries will be artificially seen to drop and the mortality rate of non-shock sepsis will appear to rise. It is important that all stakeholders understand any changes, and how they will influence data on incidence, hospital length of stay, critical care admission rates, critical care length of stay and mortality rates.

NEXT STEPS

The release of the new definitions has created confusion among both front-line healthcare workers, who need to identify patients with sepsis early in the course of the disease; and quality improvement programs which need to educate, train, plan and effect change and measure performance. Quality improvement programs require training strategies on early detection and easily applicable screening tools. The proposed variation in SOFA score as a definition of organ dysfunction is not feasible to be used at the bedside. For the new proposed score, qSOFA, to be accepted into operational use it must be adequately prospectively validated, must be evaluated and show promise as a screening tool rather than merely a risk stratification tool, and a pathway must be offered for the management of patients who are clearly unwell but who do not (yet) satisfy 2 qSOFA criteria. Some of these issues were discussed by the authors as limitations in the Sepsis 3.0 manuscript (ref). However, their statements were not sufficient to clarify how the new definitions can be used at bedside.

Thus, our proposal is that an additional statement by the Sepsis 3 authors be issued in order to clarify some of these points as stated below.

1. Different stakeholders might need to use different definitions of organ dysfunction.

The bedside physician should provide prompt care to any patient with suspected infection who has any new organ dysfunction irrespective of the SOFA score. In quality improvement programs, the broad Sepsis 3 narrative definition of sepsis, which describes the presence of any life-threatening organ dysfunction, should be considered. This would include, for instance, patients with any one of a reduced level

of consciousness, hypotension or hyperlactatemia, as all such patients require early recognition and treatment. Outside hospitals, strategies reflecting the need for a balance from specificity toward sensitivity whilst retaining the lack of requirement for laboratory tests will be needed. At the present time, a variation in SOFA score as a definition of organ dysfunction is more appropriate for use in clinical and epidemiological studies.

2. qSOFA is not part of the definition and must not be used as a screening tool for patients with sepsis. It should not become part of clinical practice before it is properly and prospectively evaluated in the different clinical settings both in terms of its predictive validity and construct validity. In settings with high mortality rates, particularly in low and middle income countries, screening for sepsis should be based on sensitive tools with a response graded according to acuity to allow earlier recognition.
3. In settings where lactate measurements are not available, the diagnosis of septic shock is compromised. The Task Force acknowledged that the voting process for the septic shock definition was a tight one. Only a slight majority of the members voted for having lactate as an obligatory requirement (the AND choice) instead of an alternative to vasopressor requirement (the OR choice). They recognized that this issue needed to be revisited soon. Meanwhile, the Task Force needs to clearly state how the diagnosis of septic shock should be made in settings where lactate is not available.
4. In future discussions, to further develop and to overcome the current controversies, it is important to be more inclusive in terms of a global perspective and stronger

involvement of all stakeholders, representative not only of the spectrum of healthcare providers but also of different cultures, economic environments and gender, which will improve the content and construct validity of future versions of the definitions.

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